THE ENDOCRINE SOCIETY

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The Endocrine Society, American Association of Clinical Endocrinologists, American Diabetes Association
Joint Statement for Health Care Providers
Re: FDA Advisory Panel Avandia Recommendation

July 13–14, 2010: Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting

- On July 14, 2010, a 33-member FDA external advisory panel (a combination of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drugs Safety and Risk Management Advisory Committee) provided mixed recommendations regarding Avandia (rosiglitazone) but voted 20 to 12 not to remove Avandia from the market. There was one abstention.

The FDA advisory panel, which was dominated by experts in statistics and epidemiology and included only a few MD's and fewer practicing endocrinologists, took this action after a two-day hearing during which it heard 18 presentations with over 500 slides from both external and FDA subject-matter experts and reviewed over 1000 pages of documents submitted in advance.

The key debate revolved around the potential cardiovascular side effects of rosiglitazone, and the advisory panel seemed divided because of conflicting data on the drug based on the existing studies, which encompassed a variety of different patient populations and study designs. The advisory panel wrestled with the limitations and strengths of the retrospective data analyses that constituted the bulk of the current information, given that there are many precedents in which such retrospective studies were not confirmed in prospective, randomized control trials. There was considerable difference of opinion among the experts on the FDA advisory panel about the appropriate interpretation of the data and their implications for patient safety.

Significant discussion also revolved around the comparison of Avandia with Actos since there are no prospective head-to-head trials comparing the two drugs and the comparisons are based on meta-analyses using different patient populations and with different designs. The Committees voted 19 to 11 (with 2 abstentions and 1 non-voting) to allow the FDA-ordered TZD Intervention with Vitamin D Evaluation (TIDE) trial to continue after a thorough discussion of its design, ethics, and progress to date. Whether or not it will be continued is unclear at this time.

The final decision of whether or not to pull the drug from the market remains with the FDA leadership, and at this time we cannot predict the FDA's final action. In view of the likelihood of a great deal of publicity about this situation, we believe that health care providers should be prepared to field calls and e-mails from their patients about what may be the best option for their glycemic management at this time. In this regard, we have attached a brief summary of some of the relevant studies.

RECOMMENDATIONS FOR HEALTHCARE PROVIDERS AND THEIR PATIENTS

In terms of what to tell patients, we refer to the joint AACE/ADA/Endocrine Society press release from the opening of the hearings which stated:

1) do not stop taking your medication without first discussing it with your endocrinologist or health care provider
2) there are alternative medications for diabetes if needed
3) retain good glucose control to avoid short and long term complications of diabetes

SUMMARY OF STUDIES

The issue of Avandia's potential risk was raised by Nissen and Wolski in a 2007 (1) meta-analysis of 42 studies which was updated in a recently published study that added an additional 14 studies (2). These studies and a similar one by the FDA staff showed an increased risk for MI (but not cardiovascular death) by Avandia. In addition, a retrospective study of the Medicare database by Graham et al. showed an increased risk of death (but not MI) for those over the age of 65 with Avandia compared with Actos (pioglitazone) (3).

The RECORD trial, which was an open-label, prospective randomized control, non-inferiority trial, showing that Avandia did not have such a risk compared to Active Comparators (4). This GSK-sponsored trial, which is the longest trial of any drug in diabetes was scrutinized in detail by the FDA and was the subjected to extensive criticism based on both design and execution and the fact that it was conducted in a relatively low risk population.

On the other hand, the meta-analyses of studies using data from Active Comparator trials rather than placebo-controlled trials showed no signal of risk from Avandia. In addition, post-hoc analysis of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study (5), a prospective randomized controlled trial in a high risk population and a similar analysis of the Veterans Administration Diabetes Trial (VADT) also showed no increase in cardiovascular risk.

(1) Nissen, S.E. and Wolski, K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Eng J Med 356, 2457-71, 2007.

(2) Nissen, SE and Wolski, K. Rosiglitazone revisited. Arch Intern Med published online June 28, 2010 doi: 10.1001/archintermed.2010.207.

(3) Graham, DJ et al., Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA published online June 28, 2010 doi: 10.1001/jama.2010.920.

(4) Home PD et al., Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a mulitcentre, randomized, open-label trial. Lancet 373, 2125-2135, 2009.

(5) Bach RG. American Diabetes Association (ADA) 2010 Scientific Sessions; June 25 - 29, 2010, Orlando, FL.